Cigna Medical Coverage Policy

Subject    Genetic Testing for Muscular Dystrophy and Spinal Muscular Atrophy

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Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. Under some benefit plans, coverage for genetic screening and/or testing may be excluded or restricted. If coverage for genetic testing is available, the following conditions of coverage apply.

Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy (BMD)
Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for DMD and BMD (gene DMD) with deletion/duplication analysis when BOTH of the following criteria are met:

- clinical findings that suggest DMD or BMD
- elevated serum creatine kinase (CK) concentration

Cigna covers carrier genetic testing as medically necessary for DMD and BMD (gene DMD) with deletion/duplication analysis for females with the capacity and desire to reproduce when BOTH of the following criteria are met:

- the female has a male first-degree relative with DMD or BMD
- a male relative with DMD or BMD is not available for testing

Cigna covers genetic testing for DMD and BMD (gene DMD) with full sequence analysis as medically necessary when deletion/duplication analysis is negative and the clinical suspicion of these conditions remains high.
Cigna covers genetic testing as medically necessary for DMD and BMD (gene DMD) for a known familial mutation (i.e., testing for the known familial variant) for EITHER of the following indications:

- preconception or prenatal genetic testing in females to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce when there is a blood relative with a gene DMD mutation who is related through the maternal line
- prenatal testing of a male fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) for the known mutation when one parent has been diagnosed with DMD or BMD or is a known carrier

**Emery-Dreifuss Muscular Dystrophy (EDMD)**

Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for EDMD with full sequence analysis (gene LMNA) in an individual with clinical findings suggestive of EDMD.

Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for EDMD with full sequence analysis (genes EMD, FLHI) when BOTH of the following criteria are met:

- individual with clinical findings suggestive of EDMD
- testing is performed in an individual where an x-linked inheritance pattern is suspected (i.e., no male to male transmission)

Cigna covers genetic testing for EDMD as medically necessary for a known familial mutation (i.e., testing for the known familial variant) for ANY of the following indications:

- predictive testing in an asymptomatic individual when a blood relative has been diagnosed with autosomal dominant or X-linked EDMD
- prenatal testing of a fetus (i.e., amniocentesis or CVS) or PGD when one parent is a known carrier of EDMD
- preconception or prenatal genetic testing in females to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce when there is a blood relative with an FLH1 or EMD gene mutation who is related through the maternal line
- carrier testing for an asymptomatic individual when there the individual has a capacity and desire to reproduce and there is a family history of autosomal recessive EDMD and a known LMNA mutation in a first or second-degree relative*

**Facioscapulohumeral Muscular Dystrophy (FSHD)**

Cigna covers confirmatory (diagnostic) genetic testing for FSHD as medically necessary with deletion testing to determine mutation of D4Z4 locus in an individual with clinical findings suggestive of FSHD.

Cigna covers genetic testing for FSHD as medically necessary for a known familial mutation (i.e., testing for the known familial variant) for EITHER of the following indications:

- predictive testing for asymptomatic individuals when there is a known mutation in a first- or second-degree relative
- prenatal testing of a fetus (i.e., amniocentesis or CVS) when one parent has a FSHD mutation

Cigna does not cover PGD for FSHD because it is considered experimental, investigational or unproven.

**Limb-Girdle Muscular Dystrophy (LGMD)**

**LGMD type 1B (LMNA Gene)**

Cigna covers genetic testing confirmatory (diagnostic) genetic testing for LGMD type 1B as medically necessary with full sequence analysis of the LMNA gene when ALL of the following criteria are met:

- family history consistent with autosomal dominant inheritance
- clinical findings consistent with a diagnosis of muscular dystrophy with proximal weakness
- elevated serum creatine kinase (CK) concentration
- muscle biopsy confirms degeneration/regeneration (i.e., dystrophic changes)

Cigna covers predictive testing for known familial mutation (i.e., testing for the known familial variant) in the LMNA gene as medically necessary for an individual with a blood relative with a LMNA mutation.

**LGMD type 2I (FKRP Gene)**
Cigna covers confirmatory (diagnostic) genetic testing for LGMD type 2I as medically necessary with full sequence analysis of the FKRP gene when ALL of the following criteria are met:

- family history consistent with autosomal recessive inheritance
- clinical findings are consistent with a diagnosis of muscular dystrophy with proximal weakness
- elevated serum creatine kinase (CK) concentration
- muscle biopsy confirms degeneration/regeneration (i.e., dystrophic changes)

Cigna covers confirmatory (diagnostic) genetic testing for LGMD type 2I as medically necessary with full sequence analysis of the FKRP gene when ALL of the following criteria are met:

- individual has a child affected with LGMD2I due to homozygous or compound heterozygous FKRP mutations
- individual has the capacity and desire to reproduce

**Myotonic Dystrophy Type 1 (DM1) and Type 2 (DM2)**
Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for DM1 (gene DMPK) with targeted mutation analysis in an individual with clinical features suggestive of DM1.

Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for DM2 (gene CNBP) with mutation analysis in an individual with clinical features suggestive of DM2.

Cigna covers as medically necessary genetic testing for DM1 and DM2 for a known familial mutation (i.e., testing for the known familial variant) for EITHER of the following indications:

- predictive testing in an asymptomatic individual ≥ age 18 when a first or second-degree relative* has been diagnosed with DM1 or DM2
- prenatal testing of a fetus (i.e., amniocentesis or CVS) or PGD for EITHER of the following:
  - one parent has been diagnosed with DM1 or DM2
  - one parent has been identified by gene DMPK molecular genetic testing to be at risk for having a child with DM1(<35 repeats)

**Spinal Muscular Atrophy (SMA)**
Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for SMA (gene SMN1) with targeted mutation analysis or gene dosage analysis in an individual with clinical features suggestive of SMA.

Cigna covers genetic testing for SMA (gene SMN1) with full sequence analysis as medically necessary for ANY of the following indications:

- when targeted mutation analysis is negative and the clinical suspicion of the condition remains high
- in an asymptomatic individual to determine carrier status for EITHER of the following indications:
  - the individual has a child with SMA and BOTH of the following:
    - child has only one deletion
    - individual has tested negative for exon 7 deletion
  - the individual has a deceased child with clinical features consistent with SMA and BOTH of the following:
    - tissue samples or blood spots from the child are not available for testing
    - individual tested negative for exon 7 deletion
Cigna covers as medically necessary genetic testing for SMA (gene SMN1) for a known familial mutation (i.e., testing for the known familial variant) for EITHER of the following indications:

- carrier testing (prenatal or preconception) when the individual has both the capacity and desire to reproduce and there is a blood relative with a confirmed SMN1 mutation
- prenatal testing of the fetus (i.e., amniocentesis or CVS) or PGD when two disease-causing mutations in the gene have been identified in the biological parents/reproductive couple

Cigna covers carrier testing (prenatal and preconception) as medically necessary for SMA (gene SMN1) by gene dosage analysis when the individual has the capacity and desire to reproduce and BOTH of the following criteria are met:

- asymptomatic individual with the capacity and intention to reproduce
- there is a family history of SMA or muscular dystrophy of unknown or unspecified type, and it is not possible to test the affected relative to identify the familial mutation

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.
A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

Cigna does not cover genetic testing with a multi-gene panel, including next-generation sequencing, for muscular dystrophy because it is considered experimental, investigational or unproven.

CIGNA does not cover genetic testing for muscular dystrophy or spinal muscular atrophy in the general population because such screening is considered not medically necessary.

Any individual undergoing genetic testing for muscular dystrophy or spinal muscular atrophy should have both pre-and post-test genetic counseling completed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

General Background
Muscular dystrophy (MD) refers to a group of more than 30 genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. These disorders vary in age of onset, severity, and pattern of affected muscles. All forms of MD grow worse as muscles progressively degenerate and weaken. Some types of MD also affect the heart, gastrointestinal system, endocrine glands, spine, eyes, brain, and other organs. Respiratory and cardiac diseases may occur, and some patients may develop a swallowing disorder. All of the muscular dystrophies are inherited and involve a mutation in one of the thousands of genes that program proteins critical to muscle integrity. The modes of inheritance for these conditions include: X-linked (or sex-linked) recessive, autosomal dominant and autosomal recessive. There are nine major groups of the muscular dystrophies. The disorders are classified by the extent and distribution of muscle weakness, age of onset, rate of progression, severity of symptoms, and family history (including any pattern of inheritance) (National Institute of Neurological Disorders and Stroke [NINDS], 2011). Spinal Muscular Atrophy (SMA) belongs to a group of hereditary diseases that cause weakness and wasting of the voluntary muscles in the arms and legs.
The disorders are caused by an abnormal or missing gene known as the survival motor neuron gene 1 (SMN1), which is responsible for the production of a protein essential to motor neurons (NINDS, 2012).

**Duchenne and Becker Muscular Dystrophy**

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy (MD) as well as the most common form of muscular dystrophies overall. They are considered dystrophinopathies which include a spectrum of muscle disease caused by mutations in gene DMD, which encodes the protein dystrophin. DMD usually presents in early childhood with delayed milestones, including delays in sitting and standing independently. Proximal weakness causes a waddling gait and difficulty climbing. DMD is rapidly progressive, with affected children being wheelchair dependent by age 12 years. Cardiomyopathy occurs in individuals with DMD after age 18 years. Few survive beyond the third decade, with respiratory complications and cardiomyopathy being common causes of death. Becker Muscular Dystrophy (BMD) is very similar to DMD; however, the symptoms are much less severe and are generally not seen until later in life. BMD is characterized by later-onset skeletal muscle weakness; individuals remain ambulatory into their 20s. The onset of BMD is usually in late childhood or adolescence, and the course is slower and less predictable than that of DMD (Darras, et al., 2011; NINDS, 2011).

DMD is the only gene in which mutations cause the dystrophinopathies. Molecular genetic testing can establish the diagnosis without a muscle biopsy in most individuals. Deletions of one or more exons will account for approximately 60-70% of mutations in individuals with these conditions. Duplications account for the disease-causing mutations in approximately 5-10% of males with these conditions. Point mutations (small deletions or insertions, single-base changes, and splicing mutations) account for approximately 25%-35% of mutations in males with DMD and about 10%-20% of males with BMD (Darras, et al., 2011).

The dystrophinopathies are inherited in an X-linked manner. The risk depends on the carrier status of the mother. Carrier females have a 50% chance of transmitting the DMD mutation in each pregnancy. Sons who inherit the mutation will be affected; daughters who inherit the mutation are carriers and may or may not develop cardiomyopathy. Males with DMD do not reproduce. Males with BMD or DMD-associated dilated cardiomyopathy (DCM) may reproduce: all of their daughters are carriers and none of their sons inherit their father's DMD mutation. Carrier testing for at-risk females and prenatal testing for pregnancies at increased risk are possible if the DMD disease-causing mutation in the family is known or if informative linked markers have been identified (Darras, et al., 2011).

Deletion/duplication analysis can detect either deletions or duplication of gene DMD in probands and carrier females. Full sequence analysis can detect point mutations. Diagnostic testing is indicated for males with clinical findings suggesting a dystrophinopathy and an elevated serum (CK) concentration. Serum CK levels varies with laboratory, but the value is approximately: males 171 U/L and females 145 U/L. In DMD, it elevated to approximately ten times the normal value; in BMD, to over five times the normal value. Deletion/duplication analysis should be performed first, and if no mutation is identified, sequence analysis can be performed. If a disease-causing DMD mutation is identified, the diagnosis of a dystrophinopathy is established, but the distinction between DMD and BMD can be difficult in some cases since there are mutations that may be found in males with DMD and BMD (Darras, et al., 2011).

**Professional Societies/Organizations—Duchenne and Becker Muscular Dystrophy:** A workshop was jointly organized and sponsored by The European Molecular Genetics Quality Network (EMQN), Euro-Gentest, TREAT-NMD published best practice guidelines on molecular diagnostics in Duchene/Becker muscular dystrophies (Abbs, et al., 2010). The guidelines include the following:

- Affected males suspected to have a dystrophinopathy based on high serum creatine kinase (CK) levels and/or muscle biopsy, are referred for a molecular confirmation of the clinical diagnosis. Molecular confirmation of a dystrophinopathy is achieved by demonstrating the presence of a clearly pathogenic variant in the DMD gene. Absence of a DMD mutation would reduce the likelihood of a patient having a dystrophinopathy, with the reduction being dependent on the sensitivity of the mutation screening procedure(s) used. It is currently not possible to refute a diagnosis of a dystrophinopathy based on the results of genetic testing, since no mutation detection protocol which is currently available can demonstrate 100% sensitivity.
- Since whole exon deletions are the predominant type of mutation in the DMD gene, an initial screen which detects the majority of deletions should be the minimum level of diagnostic test offered.
• If no deletion or duplication has been found, the clinical diagnosis cannot be confirmed nor excluded. If the clinical features, family history, and/or results of muscle biopsy suggest a dystrophinopathy, further tests should be offered to search for a pathogenic mutation.

• Prenatal diagnosis for DMD/BMD should only be carried out for male pregnancies. At present, it is not possible to predict whether a female heterozygote for a DMD mutation will manifest any signs of the disorder or not, and therefore it would be inappropriate to offer prenatal diagnosis for a female fetus.

**Emery-Dreifuss Muscular Dystrophy**

Emery-Dreifuss muscular dystrophy (EDMD) primarily affects boys. The disorder has two forms: X-linked, recessive and autosomal dominant. Onset of the condition is usually apparent by age ten, but symptoms can appear as late as the mid-twenties. This disease causes slow but progressive wasting of the upper arm and lower leg muscles and symmetric weakness. Contractures in the spine, ankles, knees, elbows, and back of the neck usually precede significant muscle weakness, which is less severe than in Duchenne MD. Contractures may cause elbows to become locked in a flexed position. The entire spine may become rigid as the disease progresses. Other symptoms include shoulder deterioration, toe-walking, and mild facial weakness. Serum creatine kinase (CK) levels may be moderately elevated. Nearly all EDMD patients have some form of heart problem by age 30, often requiring a pacemaker or other assistive device. Female carriers of the disorder often have cardiac complications without muscle weakness. Patients often die in mid-adulthood from progressive pulmonary or cardiac failure (NINDS, 2011).

The types of EDMD are distinguished by their pattern of inheritance: X-linked, autosomal dominant and autosomal recessive. Although the three types have similar signs and symptoms, researchers believe that the features of autosomal dominant EDMD are more variable than the other types. A small percentage of people with the autosomal dominant form experience heart problems without any weakness or wasting of skeletal muscles. X-linked EDMD is the most common form of this condition, affecting an estimated 1 in 100,000 people. The autosomal recessive type of this disorder appears to be very rare; only a few cases have been reported worldwide. The incidence of the autosomal dominant form is unknown.

The clinical diagnosis of EDMD is based on the presence of the following (Bonne, et al., 2010):

• Early contractures of the elbow flexors, Achilles tendons (heels), and neck extensors resulting in limitation of neck flexion, followed by limitation of extension of the entire spine

• Slowly progressive wasting and weakness typically of the humero-peroneal/scapulo-peroneal muscles in the early stages

• Cardiac disease with conduction defects and arrhythmias:
  - Atrial fibrillation, flutter and standstill, supraventricular and ventricular arrhythmias, and atrio-ventricular and bundle-branch blocks may be identified on resting electrocardiography (ECG) or by 24-hour ambulatory ECG.
  - Dilated or hypertrophic cardiomyopathy may be detected by the performance of echocardiographic evaluation.

Treatment of manifestations of the condition include surgery to release contractures and manage scoliosis as needed; aids (canes, walkers, orthoses, wheelchairs) as needed to help ambulation; treatment for cardiac arrhythmias, AV conduction disorders, congestive heart failure, including antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator (ICD); heart transplantation for the end stages of heart failure as appropriate; respiratory aids (respiratory muscle training, assisted coughing techniques, mechanical ventilation) as needed.

Mutations in the EMD, FHL1, and LMNA genes cause EDMD. Most cases of EDMD are caused by mutations in the EMD gene. Mutations in the EMD and FHL1 genes are responsible for X-linked EDMD. The gene LMNA is associated with autosomal dominant EDMD (AD-EDMD) and rare autosomal recessive EDMD (AR-EDMD) (Bonne, et al., 2010). Approximately 64% of individuals with a diagnosis of EDMD who have emerin detected on immunocytochemistry and/or immunoblotting have no mutation identified in genes EMD, FHL1, or LMNA, suggesting that these individuals are either misdiagnosed or that other as-yet unidentified genes are involved in EDMD (Bonne, et al., 2010).
Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in families with X-linked EDMD and autosomal dominant EDMD, and of the disease-causing mutations in families with autosomal recessive EDMD. For X-linked EDMD, prenatal testing for pregnancies at increased risk is possible if the EMD or FHL1 mutation has been identified in a family member. The usual procedure is to determine the sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks’ gestation or by amniocentesis usually performed at about 15 to 18 weeks’ gestation. If the karyotype is 46,XY, then DNA from fetal cells can be analyzed for the known disease-causing mutation. For AD-EDMD and AR-EDMD, prenatal diagnosis for pregnancies at increased risk is possible if the LMNA mutation has been identified in a family member (Bonne, et al., 2010).

Professional Societies/Organizations—Emery-Dreifuss Muscular Dystrophy: European Federation of Neurological Societies (EFNS): Regarding genetic testing for EDMD, the EFNS guidelines for the molecular diagnosis of neurogenetic disorders note that, “The disease is genetically heterogeneous – the main mode of transmission is X-linked. In these cases, deletions are found in a small gene on Xq28 (Emerin). Most mutations are private, i.e. different in each affected family and complete sequencing is usually necessary.” (Burgunder, et al., 2011).

Facioscapulohumeral Muscular Dystrophy
Facioscapulohumeral muscular dystrophy (FSHD) initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humera) with progressive weakness. Also known as Landouzy-Dejerine disease, this third most common form of muscular dystrophy is an autosomal dominant disorder. Most individuals have a normal life span, but some individuals become severely disabled. Disease progression is typically very slow, with intermittent spurts of rapid muscle deterioration. Onset is usually in the teenage years but may occur as late as age 40. Muscles around the eyes and mouth are often affected first, followed by weakness around the lower shoulders and chest. A particular pattern of muscle wasting causes the shoulders to appear to be slanted and the shoulder blades to appear winged. Muscles in the lower extremities may also become weakened. Reflexes are impaired only at the biceps and triceps. Changes in facial appearance may include the development of a crooked smile, a pouting look, flattened facial features, or a mask-like appearance. Some individuals cannot pucker their lips or whistle and may have difficulty swallowing, chewing, or speaking. In some individuals, muscle weakness can spread to the diaphragm, causing respiratory problems. Other symptoms may include hearing loss (particularly at high frequencies) and lordosis, an abnormal swayback curve in the spine. Some FSHD patients feel severe pain in the affected limb. Cardiac muscles are not affected, and the pelvic girdle is rarely significantly involved. An infant-onset form of FSHD can also cause retinal disease and some hearing loss (NINDS, 2011).

The FSHD genetic defect does not reside in mutation of any protein-coding gene. FSHD results from a deletion of genetic material from a region of DNA known as D4Z4. This region is located near one end of chromosome 4. The D4Z4 region normally consists of 11 to more than 100 repeated DNA segments, each of which is about 3,300 DNA base pairs (3.3 kb) long. However, in people with facioscapulohumeral muscular dystrophy the D4Z4 region on one copy of chromosome 4 is abnormally short, containing between 1 and 10 repeats. It is uncertain how a shortened D4Z4 region causes progressive muscle weakness and wasting. Researchers suspect that genetic factors other than the shortened D4Z4 region may also be involved in this condition (Lemers, et al., 2012).

Deletion testing will detect 95% of contraction mutation of D4Z4 locus. Alternative methods are in process of being developed to improve detection of pathologic alleles. Haplotype analysis or analysis to confirm that the D4Z4 contraction mutation occurred on a permissive haplotype 2 is generally not informative and not available (Lemers, et al., 2012).

Prenatal testing for pregnancies at increased risk is possible if the D4Z4 contraction mutation has been identified in the family (Lemmers, et al., 2012). Prenatal testing is available for pregnancies at 50% risk for FSHD analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling (CVS) (Lemmers, et al., 2012).

There is no method for preimplantation genetic diagnosis (PGD) for FSHD is currently reliable or available (Lemmers, et al., 2012).
Professional Societies/Organizations—Facioscapulohumeral Muscular Dystrophy:
An international workshop published standards of care and management of FSHD (Tawil, et al., 2010). The report included:

- In patients of suspected FSHD, genetic confirmation can be performed with various methods.
- Potential pitfalls in the genetic diagnosis of FSHD, that affects a minority (<5%) of patients.
- Prenatal diagnosis is available for FSHD based on genetic tests uses for diagnostic testing,

Limb-Girdle Muscular Dystrophy
Limb-girdle muscular dystrophy (LGMD) is a descriptive term, generally reserved for childhood- or adult-onset muscular dystrophies that are distinct from the much more common X-linked dystrophinopathies, which include Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) (both affected males and symptomatic females). The term LGMD1 (including, e.g., LGMD1A, LGMD1B) refers to genetic types showing dominant inheritance, whereas LGMD2 refers to types with autosomal recessive inheritance. Mutations at more than 50 loci have been shown to cause LGMD (Pegoraro, et al., 2012).

Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal. Proximal weakness refers to weakness of the muscles closer to the center of the body (including the shoulder, pelvic girdle, upper thighs, and upper arms). Distal weakness refers to weakness in muscles farther from the center of the body (including lower legs and feet, lower arms and hands). Onset, progression, and distribution of the weakness and wasting may vary considerably among individuals and genetic subtypes. LGMDs are typically nonsyndromic, with clinical involvement typically limited to skeletal muscle (Pegoraro, et al., 2012).

The limb-girdle dystrophies typically have degeneration/regeneration (dystrophic changes) on muscle biopsy, which is often associated with elevated serum creatine kinase (CK) concentration. As part of diagnostic process, it is necessary to first rule out an X-linked dystrophinopathy (e.g., Duchenne and Becker Muscular Dystrophy). Biochemical testing (i.e., protein testing by immunostaining or immunoblotting) performed on muscle biopsy can assist in establishing the diagnosis of some LGMD types (Pegoraro, et al., 2012).

There are no definitive treatments for the limb-girdle muscular dystrophies. Management should be tailored as to each individual and each specific LGMD type. Management to prolong survival and improve quality of life may include: weight control to avoid obesity, physical therapy and stretching exercises to promote mobility and prevent contractures, use of mechanical aids to help ambulation and mobility, surgical intervention for orthopedic complications, use of respiratory aids when indicated, monitoring for cardiomyopathy in LGMD types with cardiac involvement, and social and emotional support and stimulation (Pegoraro, et al., 2012).

Type of limb-girdle muscular dystrophy is categorized by mode of inheritance and molecular genetics. There are over 20 genes that have been identified as responsible for autosomal dominant and recessive LGMD. The recessive LGMD occurs more frequently than the dominant forms, and usually begins in childhood or teenage years. The autosomal dominant form usually begins in adulthood. In general, the more clinical signs appear, the more rapid the rate of disease progression.

Mutations in the LMNA gene cause limb-girdle muscular dystrophy type 1B. Limb-girdle muscular dystrophy type 1C is one of a group of muscle disorders called caveolinopathies caused by mutations in the CAV3 gene. Limb-girdle muscular dystrophy type 2 includes forms of the disorder that have an inheritance pattern called autosomal recessive. Calpainopathy, or limb-girdle muscular dystrophy type 2A, is caused by mutations in the CAPN3 gene. Type 2A is the most common form of limb-girdle muscular dystrophy, accounting for about 30 percent of cases. Dysferlinopathy, also called limb-girdle muscular dystrophy type 2B, is caused by mutations in the DYSF gene. Sarcoglycanopathies are forms of limb-girdle muscular dystrophy caused by mutations in the SGCA, SGCB, SGCG, and SGCD genes. These sarcoglycanopathies are known as limb-girdle muscular dystrophy types 2D, 2E, 2C, and 2F respectively. A TTN gene mutation causes limb-girdle muscular dystrophy type 2J, which has been identified only in the Finnish population. Mutations in the ANO5 gene cause limb-girdle muscular dystrophy type 2L. Mutations in several other genes cause forms of limb-girdle muscular dystrophy called dystroglycanopathies, including limb-girdle muscular dystrophy types 2I, 2K, 2M, and 2N. Other rare forms of limb-girdle muscular dystrophy are caused by mutations in several other genes, some of which have not been identified (Genetics Home Reference, 2011).
Changes in these genes are associated with limb-girdle muscular dystrophy: ANO5, CAPN3, CAV3, DYSF, FKRP, FKTN, LMNA, MYOT, POMGNT1, POMT1, POMT2, SGCA, SGCB, SGCD, SGCG, TCAP, TRIM32, and TTN. While testing for the genes involved in LGMD is available, the use of molecular genetic testing to establish the specific type of LGMD is challenging for several reasons including the following:

- There are many genes are involved.
- Mutations in no one gene account for the majority of cases.
- Few clinical or laboratory findings help identify the associated gene for a given individual.
- The lack of common mutations prevents efficient screening by genotype.
- About 50% of currently identified LGMD would have no molecular diagnosis, even if all 20 currently known genes were fully sequenced.

(Pegoraro, et al., 2012)

Since there are many genes involved in this conditions and testing is not conclusive for the diagnosis of the condition, the clinical utility of genetic testing for most LGMD has not been established.

There are a few specific circumstances where targeted LGMD genetic testing may have significant impact on medical management as cardiac involvement is seen in affected patients. In these situations genetic testing may be considered.

- a recessive form of LGMD (LGMD2I) caused by mutations in the FKRP gene
- a dominant form of LGMD (LGMD1B) caused by mutations in the LMNA gene

LGMD patients with mutations in the FKRP or LMNA genes should be managed by a cardiologist, with routine surveillance for cardiomyopathy, including ECG and echocardiograms performed.

LGMD2I, caused by mutations in the FKRP gene, presently accounts for about 6% of LGMD autosomal recessive diagnoses (Pegoraro, et al., 2012). The LGMD2I (FKRP) phenotype ranges from severe (similar to Duchenne muscular dystrophy) to mild with no clinically apparent skeletal muscle involvement (Muller, et al., 2005; Boito, et al., 2005). Most importantly, cardiac involvement occurs in 10%–55% of affected individuals (Pegoraro, et al., 2012).

LGMD1B is caused by mutations in the LMNA gene, although LMNA mutations result in at least 11 allelic conditions, including well-described hereditary cardiac conditions. In LGMD1B, muscle weakness and cardiac involvement are present by the third decade. Mutations in this gene can lead to severe cardiac events and sudden death (Pegoraro, et al., 2012). Left ventricular hypertrophy and atroventricular conduction defect are common and can progress to second-degree heart block requiring a pacemaker, and rarely dilated cardiomyopathy is present. In individuals identified with a LMNA mutation requiring pacemaker placement (i.e. history of arrhythmia or known risk of arrhythmia), the use of a pacing ICD rather than a pacemaker has been recommended due to the risk of ventricular arrhythmias and sudden death (Hershberger, et al., 2009).

Myotonic dystrophy types 1 (DM1) and 2 (DM2)
Myotonic dystrophy types 1 (DM1) and 2 (DM2) are forms of muscular dystrophy. DM1 may be referred to as Steinert syndrome, dystrophia myotonica, myotonia atrophica, myotonia dystrophica, Steinert disease, or Steinert myotonic dystrophy syndrome. DM2 may also be referred to as proximal myotonic myopathy (PROMM), myotonic myopathy, and proximal Ricker syndrome. Myotonic dystrophy is the most common adult form of muscular dystrophy. These conditions are multisystem disorders that affect skeletal muscle and smooth muscle, as well as the eye, heart, endocrine system and central nervous system (CNS). They share the same core diagnostic criteria and multi-organ involvement but there are clinical aspects that are specific to each type (Botta, et al., 2006).

There are three overlapping forms of DM1 (Bird, 1999/2011):

- Mild DM1: Individuals with mild DM1 may have only cataract, mild myotonia, (i.e., sustained muscle contraction) or diabetes mellitus. These individuals may have a normal or minimally shortened life span.
- Classic DM1: The age of onset for classic DM1 is generally in the 20s and 30s and less commonly after age 40 years. At times, it may be evident in childhood with subtle signs such as myotonic facies and myotonia observe. The predominant symptom is distal muscle weakness, leading to foot drop/gait
disturbance and difficulty with tasks that require fine dexterity. Some individuals may have ophthalmoplegia, and others may exhibit dysarthria with nasal speech. Eventually, cataracts may be observed by slit lamp examination in nearly all affected individuals. Cardiac conduction defects may occur. Rarely, this form will progress to the point of wheelchair confinement. Women with DM1 are at risk for complications during pregnancy.

- **Congenital DM1:** This form often presents before birth as polyhydramnios and reduced fetal movement. After delivery, main features include severe generalized weakness, hypotonia and respiratory compromise. Mortality from respiratory failure is high. A gradual increase in motor function may occur in surviving infants. As in the classic form, progressive myopathy may eventually occur. In 50–60% of affected individuals, an intellectual disability may be present.

DM2 is generally less heterogeneous in its presentation than DM1. The clinical course of DM2 is generally more favorable as compared to DM1 (Udd, et al., 2006). The onset of symptoms of DM2 is generally in the third decade. The most common symptoms are muscle weakness and pain, although there have been reports of myotonia in the first decade. Unlike DM1, which can present in adulthood or during infancy or childhood with variable severe congenital features, DM2 has not been reported to be associated with developmental abnormalities and severe childhood symptoms (Dalton, et al., 2006/2007). No congenital form has yet been described in the literature (Botta, et al., 2006).

There is no specific treatment for the progressive weakness in individuals with myotonic dystrophy. Management may include consultation with a physiatrist, occupational therapy, or physical therapy for evaluation for orthoses and assistive devices. Electrocardiogram (ECG), Holter monitoring and an echocardiogram should be performed to evaluate syncope, palpitations and other symptoms of potential cardiac origin. When cardiac symptoms or ECG evidence of arrhythmia are present, consultation with a cardiologist is strongly recommended because fatal arrhythmias can occur prior to other symptoms.

The nonmolecular tests that were used in the past to establish the diagnosis of DM1 and DM2 currently play little role in diagnosis. To the extent that they are still used, they are primarily employed when molecular testing of either myotonic dystrophy protein kinase (DMPK) gene or the gene encoding zinc finger protein 9 (CNBP, also known as gene ZNF9), are normal and other myopathies are under consideration. These tests may include: electromyography (EMG), serum creatine kinase (CK) concentration, and muscle biopsy (Bird, 1999/2011; Dalton, et al., 2006/2007). Muscle biopsy cannot distinguish between the two types of myotonic dystrophy. The diagnosis of myotonic dystrophy is confirmed by molecular genetic testing. The DMPK gene is the only gene associated with DM1. CNBP is the only gene known to be associated with DM2. Both types of myotonic dystrophy are inherited in an autosomal dominant manner. Offspring of an individual with an expanded allele have a 50% chance of inheriting the mutant allele.

Molecular genetic testing detects mutations in nearly 100% of affected individuals with DM1 and is clinically available. Essentially, 100% of individuals with DM1 have an increased number (i.e., an expansion) of the cholesterol triglyceride trinucleotide repeat in the DMPK gene. Direct analysis of the cytosine-thymidine-guanine (CTG) repeat expansions is so sensitive and specific that the combination of southern blot and polymerase chain reaction (PCR) can detect all DM1 mutations without false-positives (International Myotonic Dystrophy Consortium [IDMC], 2000).

The clinical uses of molecular genetic testing for DM1 and DM2 include diagnostic, predictive, prenatal and preimplantation genetic diagnosis (PGD). Testing with targeted mutation analysis has 100% detection frequency for gene DMPK. Mutation analysis has a 99% detection frequency for gene CNPB. Predictive testing for at-risk asymptomatic individuals, prenatal and PGD requires prior identification of the disease-causing mutation in the family. Testing of at-risk asymptomatic individuals during childhood is not recommended for adult-onset conditions in which there is no known effective treatment that prevents the disease or improves the outcome. Children who are symptomatic usually benefit from having a specific diagnosis established (Dalton, et al., 2006/2007; Bird, 1999/2011). Individuals with CTG expansions in the premutation range have not been reported to have symptoms, but their children are at increased risk of inheriting a larger repeat size and thus having symptoms.

Because diagnostic gene test results have direct implications for other family members (siblings and children), genetic counseling should be made available to the person who had the gene test and also to any other interested family members. In addition, individuals who have asymptomatic testing should always have genetic
counseling with a qualified counselor to assure that the subject understands risks and benefits of testing (IDMC, 2000; Dalton, et al., 2006/2007).

The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy (Bird, 1999/2011; Dalton, et al., 2006/2007). The overlapping ranges, as well as the uncertainty regarding somatic mosaicism and in utero instability of the expanded CTG repeat, make it impossible to predict accurately whether the fetus will have congenital or adult onset DM1 (Bird, 1999/2011). Although the prenatal diagnosis is based on direct detection of the mutation, analysis of DNA from both parents may be required to exclude maternal contamination in the fetal DNA sample and, in some cases, to verify the PCR results.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family. Preimplantation genetic diagnosis (PGD) refers to genetic testing of an early embryo resulting from in vitro fertilization. PGD is available for families in which DM1 has been diagnosed in one of the parents.

Professional Societies/Organizations—Myotonic Dystrophy: The American College of Medical Genetics (ACMG) published technical standards and guidelines for myotonic dystrophy type 1 testing (Prior, 2009). The guidelines note that testing indications include: symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member. The testing may also be used for prenatal testing for at-risk pregnancies.

The International Myotonic Dystrophy Consortium (IDMC) established nomenclature and genetic testing guidelines for DM1. The IDMC guidelines note that as the correlation between expansion size and symptom severity is not absolute, it is not appropriate to offer a prediction of prognosis based on the expansion size. The testing guidelines include the following indications for genetic testing (IDMC, 2000):

- Confirmatory or symptomatic testing:
  - To confirm the clinical diagnosis: The gene test will increase the physician’s confidence in diagnosing a patient with typical symptoms.
  - To clarify an uncertain clinical diagnosis: The gene test will be useful for individuals in whom DM1 is part of a wider differential diagnosis.
- Asymptomatic or preclinical testing:
  - To determine which relative of a proband has the DM1 gene mutation: This information is important in genetic counseling.
  - To modify the a priori risk of inheriting the DM1 allele
- Testing of minors:
  - Unless there is a medically compelling reason, minors (children under the legal age) should not be tested. This is to ensure that the person tested fully understands the risks and benefits of testing.
  - Exceptions might be appropriate in the case of a symptomatic minor for whom confirmatory testing is necessary and for prenatal testing.
  - If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk.
- Prenatal testing:
  - If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk.
  - If a parent is at 50% risk and asymptomatic, the best approach is a two-step process by which the at-risk parent is tested first and prenatal testing done subsequently (if still necessary).

Spinal Muscular Dystrophy (SMA)
SMA is an autosomal recessive neurodegenerative disease that resulting from degeneration of the spinal cord motor neurons and leads to progressive muscle weakness. Onset ranges from before birth to adolescence or young adulthood. Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications. Before the genetic basis of SMA was understood, it was classified into clinical subtypes; however, it is now apparent that the phenotype of SMA associated with disease-causing mutations of the SMN1 gene spans a continuum without clear delineation of subtypes. Nonetheless, classification by age of onset and maximum function achieved is useful for prognosis and management: SMA type 1 (i.e., infantile SMA, Wernig-Hoffman disease), SMA type 2 (intermediate SMA), SMA type 3 (i.e., juvenile SMA, Kugelberg-Welander
disease), and SMA type 4 (adult-onset SMA, pseudomyopathic SMA) (Prior, et al., 2013; American College of Obstetricians and Gynecologists [ACOG], 2009).

Genetic testing is the primary means of confirming a diagnosis. The nonmolecular tests that were used in the past to establish the diagnosis of SMA currently play little role in diagnosis. Electromyography, nerve conduction studies and nerve and muscle histology may have a useful in cases when there is clinic suspicion of the condition, but the genetic testing is negative. There is no effective treatment for the disease. Management involves treatment of the manifestations of the condition including: placement of a gastrostomy tube when there are nutrition concerns; for respiratory function deterioration, tracheotomy or non-invasive respiratory support; sleep disorder breathing can be treated with nighttime use of continuous positive airway pressure; and, surgery may be considered for scoliosis in individuals with SMA 2 and SMA 3 (Prior, et al., 2011a).

Spinal muscular atrophy (SMA) is caused by a deletion of, or mutations in the survival motor neuron (SMN1) gene. This gene is responsible for the production of a protein essential to motor neurons. More than 95%–98% of individuals with SMA are homozygous for a deletion (exon 7) or truncation of SMN1. Approximately less than 4% of cases are due to new mutation in egg or sperm. Targeted mutation analysis will detect 95-98% of the deletion of exon 7 of gene SMN1. Full sequence analysis may be used when targeted mutation analysis is negative and the clinical suspicion of the condition remains high, approximately 2-5% of cases of SMA. Targeted mutation analysis is not reliable for carrier detection because it does not quantitate the number of SMN1 copies. Some laboratories may offer a polymerase chain reaction (PCR)-based dosage assay, called "SMA carrier testing" or "SMN1 dosage analysis" that is able to determine the number of SMN1 copies, thus permitting highly accurate carrier detection (Prior, et al., 2013).

The carrier frequency has been estimated to be one in fifty. Approximately 2% of carriers have mutation not detected by quantitative PCR assay. Due to this, negative genetic testing can reduce but not eliminate the change of having a child with SMA.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family. PGD may be available for families in which the disease-causing SMN1 mutations have been identified in the biologic parents.

Although there is no curative treatment for spinal muscular atrophy (SMA), confirmatory, preconception carrier status testing, prenatal testing of the fetus and PGD allow affected individuals, parents and families to establish a supportive treatment plan and to make informed reproductive choices.

Professional Societies/Organizations—Spinal Muscular Dystrophy (SMA): American College of Medical Genetics (ACMG): The ACMG technical standards and guidelines for spinal muscular atrophy testing included the following recommendations (Prior, et al., 2011):

- Testing by SMN1 deletion or copy number analysis is indicated for individuals with a suspected diagnosis of SMA presenting with symptoms of proximal muscle weakness, fasciculations, dysphagia, dysarthria, and absent deep tendon reflexes.
- Carrier testing should be offered to asymptomatic individuals with a confirmed or suspected family history of SMA.
- A prerequisite for prenatal testing is the previous identification of the homozygous deletion in the proband or positive carrier status in the parents.
- Formal genetic counseling services must be made available to anyone requesting this testing.

American College of Obstetricians and Gynecologists (ACOG): A Committee Opinion on SMA included the following recommendations (ACOG, 2009):

- Preconception and prenatal screening for SMA is not recommended in the general population at this time.
- Genetic counseling and SMA carrier screening should be offered to the following:
  - Those with a family history of SMA or SMA like disease
  - Those who request SMA carrier screening and have completed genetic counseling that includes discussion of the sensitivity, specificity, and limitations of screening
- All identified carriers for SMA should be referred for follow-up genetic counseling for a discussion of risk to the fetus and future pregnancies. Prenatal and preimplantation diagnosis should be discussed.
• Patients requesting fetal testing for SMA should be referred to an appropriate provider of prenatal genetic counseling and testing services.

European Federation of Neurological Societies (EFNS): Regarding genetic testing for spinal muscular atrophy (SMA), the EFNS guidelines for the molecular diagnosis of neurogenetic disorders note that, “Screening for SMN1 deletions is indicated in SMA I-III to confirm the diagnosis and provide genetic counseling.” (Burgunder, et al., 2011)

Multi-Gene Panel Testing for Muscular Dystrophy
Multi-gene testing or screening with a panel of genetic tests has been proposed for to test for many causes of muscular dystrophy. Panels vary by methods used and genes included; thus, the ability of a panel to detect a causative mutation(s) in any given individual with muscular dystrophy also varies.

Available multi-gene screening panels include, but are not limited to:
• Muscular Dystrophy Next Generation Sequencing Panel (Boston Children’s Hospital): this test uses massive parallel sequencing technology to identify point mutations, small deletions and insertions, and splice site mutations the test will look for mutations in the ten genes that are most frequently causative of childhood-onset muscular dystrophy including CAPN3, CAV3, DMD, FKRP, LMNA, SGCA, SGCB, SGCD, SGCG, TRIM32
• Neuromuscular Disorders Panel (Emory Genetics Laboratory): this is a 50-gene neuromuscular disorders panel includes testing for genes in many categories, including nemaline, myopathy, limb girdle muscular dystrophy, Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy, peroxisome biogenesis disorders Zellweger syndrome spectrum, and cardiomyopathies. Individual disorders included on this panel are myoadenylate deaminase deficiency, erythrocyte AMP deaminase deficiency, myofibrillar myopathy, Duchenne/Becker muscular dystrophy, congenital disorder of glycosylation type 1a, malignant hyperthermia susceptibility, myoclonus dystonia, Marinesco-Sjogren syndrome, and distal arthrogryposis. It includes genes: ACTA1, AMPD1, AMPD3, CAPN3, CAV3, COL6A1, COL6A2, COL6A3, DES, DMD, DYSF, EMD, FKRP, FKTN, ITGA7, LAMA2, LARGE, LMNA, MYOT, NEB, PEX1, PEX12, PEX14, PEX2, PEX26, PEX3, PEX5, PEX6, PLEC, PMM2, POMGNT1, POMT1, POMT2, RYR1, RYR2, SEPN1, SGCA, SGCB, SGCD, SGCE, SGCG, SIL1, TCAP, TNNT1, TNNT1, TPM2, TPM3, TRIM32, TTN, ANO5.

The use of this testing method for muscular dystrophies is still preliminary and is not yet recommended. There is insufficient evidence in the published scientific literature to establish the diagnostic and clinical utility of multi-gene testing for this condition.

Use Outside of the US
Guidance for genetic testing for several conditions reviewed in the Coverage Policy has been published by professional societies/organization.

Summary
Muscular dystrophy (MD) refers to a group of more than 30 genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. The conditions include: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), Emery-Dreifuss muscular dystrophy (EDMD), Facioscapulohumeral muscular dystrophy (FSHD), Limb-Girdle muscular dystrophy (LGMD), and Myotonic dystrophy types 1 (DM1) and 2 (DM2).

Genetic testing for DMD and BMD includes confirmatory or diagnostic testing, carrier testing, prenatal testing of a male fetus and preimplantation genetic diagnosis (PGD).

Genetic testing for EDMD includes confirmatory or diagnostic testing, predictive testing, prenatal testing and PGD.

Genetic testing for FSHD includes confirmatory or diagnostic testing, predictive and prenatal testing. A method for PGD for FSHD is not currently reliable and available.

The clinical utility of genetic testing for LGMD has not been established for most forms of LGMD. There are two specific circumstances where targeted LGMD genetic testing may have significant impact on medical
management as cardiac involvement is seen in affected patients. Genetic testing may be considered for: a recessive form of LGMD (LGMD2I) caused by mutations in the FKRP gene and a dominant form of LGMD (LGMD1B) caused by mutations in the LMNA gene.

The clinical utility of genetic testing for spinal muscular atrophy (SMA) is considered appropriate to confirm the diagnosis of spinal muscular atrophy (SMA) in order to establish supportive treatment options. Genetic testing also assists in informed reproductive planning with prenatal and preconception carrier testing, and prenatal testing of the fetus and preimplantation genetic diagnosis.

Molecular genetic testing for (DM1) and 2 (DM2) includes: confirmatory or diagnostic testing; predictive testing of asymptomatic relatives of the proband who are ≥ age 18; and prenatal and preimplantation genetic diagnosis testing which, if a parent has already been diagnosed with DM1 or DM2 or has a DM1 premutation allele can be used to assess fetal risk.

### Coding/Billing Information

**Note:**
1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary when used to report testing of the covered genes for the associated covered diagnoses:**

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<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tr>
<td>81161</td>
<td>DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed.</td>
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<td>81400</td>
<td>Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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<td>- SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy), exon 7 deletion</td>
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<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
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<td>- CNBP (CCHC-type zinc finger, nucleic acid binding protein) (eg, myotonic dystrophy type 2), evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>- DMPK (dystrophia myotonica-protein kinase) (eg, myotonic dystrophy, type 1), evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>- SMN1/SMN2 (survival of motor neuron 1, telomeric/survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy), dosage analysis (eg, carrier testing)</td>
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<td>- SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy), known familial sequence variant(s)</td>
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<td>- Known familial variant not otherwise specified, for gene listed in Tier 1 or Tier 2, DNA sequence analysis, each variant exon</td>
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<td>- DMPK (dystrophia myotonica-protein kinase) (eg, myotonic dystrophy type 1), characterization of abnormal (eg, expanded) alleles</td>
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<td>- EGR2 (early growth response 2) (eg, Charcot-Marie-Tooth), full gene sequence</td>
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<td>- EMD (emerin) (eg, Emery-Dreifuss muscular dystrophy), duplication/deletion analysis</td>
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<td>- FHL1 (four and a half LIM domains 1) (eg, Emery-Dreifuss muscular dystrophy), full gene sequence</td>
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<td>- FKRP (Fukutin related protein) (eg, congenital muscular dystrophy type 1C [MDC1C], limb-girdle muscular dystrophy [LGMD] type 2I), full gene sequence</td>
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<td>- FSHMD1A (facioscapulohumeral muscular dystrophy 1A) (eg, facioscapulohumeral muscular dystrophy), evaluation to detect abnormal (eg, deleted) alleles</td>
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<td>- FSHMD1A (facioscapulohumeral muscular dystrophy 1A) (eg, facioscapulohumeral muscular dystrophy), characterization of haplotype(s) (ie, chromosome 4A and 4B haplotypes)</td>
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<td>- LMNA (lamin A/C) (eg, Emery-Dreifuss muscular dystrophy [EDMD1, 2 and 3] limb-girdle muscular dystrophy [LGMD] type 1B, dilated cardiomyopathy [CMD1A], familial partial lipodystrophy [FPLD2]), full gene sequence</td>
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- DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy), full gene sequence

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**Experimental/Investigational/Unproven/Not Covered:**

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<td>- CAV3 (caveolin) (eg, CAV3-related distal myopathy, limb-girdle muscular dystrophy type 1C), full gene sequence</td>
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<td>- SGCG (sarcoglycan, gamma [35kDa dystrophin-associated glycoprotein]) (eg, limb-girdle muscular dystrophy), duplication/deletion analysis</td>
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<td>- FKTN (fukutin) (eg, limb-girdle muscular dystrophy [LGMD] type 2M or 2L), full gene sequence</td>
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<td>- MYOT (myotilin) (limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- SGCA (sarcoglycan, alpha [50kDa dystrophin-associated glycoprotein]) (eg, limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- SGCB (sarcoglycan, beta [43kDa dystrophin-associate glycoprotein]) (eg, limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- SGCD (sarcoglycan, delta [35kDa dystrophin-associate glycoprotein]) (eg, limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- SGCG (sarcoglycan, gamma [43kDa dystrophin-associate glycoprotein]) (eg, limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- ANO5 (anoctamin 5) (eg, limb-girdle muscular dystrophy), full gene sequence</td>
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<td>- CAPN3 (Calpain 3) (eg, limb-girdle muscular dystrophy [LGMD] type 2A, calpainopathy), full gene sequence</td>
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<td>- POMGNT1 (protein 0-linked mannose beta 1,2-N acetylglicosaminyltransferase) (eg, muscle-eye-brain disease, Walker-Warburg syndrome, full gene sequence)</td>
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sequence

81408 Molecular pathology procedure, Level 9 (eg, analysis of > 50 exons in a single gene by DNA sequence analysis)
- DYSF (dysferlin, limb girdle muscular dystrophy 2B [autosomal recessive]) (eg, limb-girdle muscular dystrophy), full gene sequence


References


